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Theoretical and Practical Considerations on the Problem of Metal–Metal Interaction

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The interaction between two metals, which can be either synergistic or antagonistic, implies that the behavior of one is changed by the presence of the other. Possible mechanisms of these interactions, which include chemical association, competition for carriers, metabolic changes, induction of binding proteins, membrane alterations are discussed.

The interactions between toxic compounds is a loose term which implies that the behavior or effect of one compound is changed by the administration or presence of another. It does not imply that the two compounds interact chemically, although chemical reaction between them or their metabolites is possible. Studies on the interaction between metals are only in an early phase and do not permit the development of generalizations or classifications.

Reaction between Two Metals

The simplest form of interaction between two metals is a chemical reaction, either without or after a chemical transformation, which can be a change in the oxidation state of the metal or, in the case of organometallic compounds, a change in, or cleavage of, the organic radical. If the *in vitro* conditions do not favor the formation of an insoluble complex between a cationic and anionic species of two metals, such complexes may be formed *in vitro* due to change in pH or the oxidation state of at least one of the metals. The indication of such a reaction is their increased retention at the injection site when they are administered simultaneously. It is essential, however, that the dose should be low enough to minimize the danger of local tissue damage, as injury can affect absorption (*1*) without there being any interaction. Thus local tissue injury certainly contributed to the increased retention of selenium at the subcutaneous injection site caused by 28.5–228 μmole/kg Cd^{2+} (*2*). When 8.0 μmole/kg Cd^{2+} is injected with an equimolar dose of selenite, however, the retention of selenium is increased only slightly and the retention of Cd^{2+} not at all (*3*), thus refuting the theory of complex formation. When, however, 2.5 μmole/kg Hg^{2+} is administered with an equimolar dose of selenite, the retention of both ions is increased (*3*). Thus selenite may react with Hg^{2+} but not with Cd^{2+} at the injection site. As mercury selenite precipitates at a lower pH than cadmium selenite (*4*), the probability of the formation *in vivo* of the former may be higher than of the latter.

Change in the oxidation state of one metal may favor reaction with another metal, outside the injection site. The conversion of hexavalent selenium to bivalent selenium allows the formation of insoluble metal selenides and, in rats given Hg^{2+} and selenate, black particles that contain mercury and selenium in a 1:1 ratio occur in macrophages and intranuclearly in the renal paroximal tubular cells (*5*). The formation of mercury selenide supposes not only the reduction of selenate or selenite, but also the concurrent presence of Hg^{2+} to react with selenide. Similar particles have not been found in rats given selenate with Cd^{2+} or tellurate and Hg^{2+} (*5*), and thus under these circumstances, the heavy metal may not be available when and where selenide is formed.

Selenium and tellurium differently affect the distribution of Hg^{2+}. Thus uptake of Hg^{2+} by the liver

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is increased by selenium and in the first 24 hr is unaffected by tellurium, whereas uptake by the kidney is decreased by selenium and increased by tellurium (*6*). The difference in these effects might be explained by the higher reduction potential of SeO_3^{2-} compared with that of TeO_3^{2-}. If the formation of selenide is faster than the formation of telluride and the presence of Hg^{2+} is not a limiting factor, the formation of colloidal particles, which favors deposition in the reticuloendothelial system, must be faster for HgSe than for HgTe.

Competition for Carriers

Although cations, such as Cd^{2+}, Hg^{2+}, and Zn^{2+}, cannot form complexes with one another, the retention of any of them is increased by the presence of one of the other two (*7*). A likely explanation for this type of interaction is the depletion of carriers. This would explain why the retention of Hg^{2+} is increased in the absence of any other metal when the dose is increased from 2.5 to 5.0 μmole/kg Hg^{2+} (*7*).

Many of the metals with known interactions, e.g., Cd^{2+}, Hg^{2+}, Pb^{2+}, Zn^{2+}, and selenium, can react with thiol groups. If diffusible thiol compounds contribute to their transport, interaction can be mediated through competition for the same carrier. Thus the retention of Cd^{2+} at the injection site is increased by Hg^{2+} more than the retention of Hg^{2+} by Cd^{2+}, and the retention of Zn^{2+} by Hg^{2+} increased more than by Cd^{2+} (*7*).

Change in the absorption can affect organ distribution. Thus Hg^{2+} decreases the liver content of cadmium by 24% 48 hr after their simultaneous administration, but the difference becomes nonsignificant when expressed in per cent of the absorbed Cd^{2+} instead of in per cent of the dose (*7*). Moreover, if the metals are injected intraperitoneally and the Hg^{2+} to Cd^{2+} ratio is increased from 1:1 to 10:1 or more, the liver uptake of Cd^{2+} increases (*8*).

Zinc and copper which, given in 100–400 times molar excess to Cd^{2+}, increase the liver uptake of cadmium at 24 hr. Although at this time Cu^{2+} and Zn^{2+} would have increased the thionein concentration in liver, the possibility cannot be dismissed that the transport of Cd to the liver cells was also influenced. For example, it has been known that the liver uptake of bilirubin or bromsulfophthahalein is fcilitated by their binding to albumin in the plasma (*9*).

Competition for extracellular carrier proteins can contribute to the interactions involving transport and this will depend upon dose and the route of administration. Selenium, which increases the binding affinities of serum proteins for Hg^{2+} (*10*) also increases the blood concentration and liver uptake of Hg^{2+} (*3*). However, increase in the blood concentration by selenium is mainly due to its increase in the packed cells (*11*). The binding of methylmercury to serum proteins is not affected by selenium (*10*) and selenium decreases the blood concentration of methylmercury with a slight decrease in liver uptake (*12*).

Interaction may occur on the albumin molecule by competition between Cu^{2+} and Zn^{2+} for common binding sites (*13*). As, at physiological concentrations and pH, preferential binding of cations to proteins is favored by cooperation between several amino acid residues, interactions may occur not only by competition for the same site, but also by a change in the affinity of one site for a given cation in consequence of the binding of another at a different site.

The mechanism whereby selenium affects the binding of mercury or cadmium is at present not fully understood but, as a first step, selenite must be metabolized in the red blood cells, after which selenium and Hg^{2+} (*14*), or selenium and Cd^{2+} (*15*), are bound in a 1:1 ratio to some plasma proteins.

In the intestine, proteins seem to regulate the absorption of some metallic cations. Antagonism by cadmium and zinc of the absorption of copper has been attributed to competition for thionein in the intestinal mucosa (*13*). It seems now, however, that intestinal Zn^{2+} and Cu^{2+} binding proteins are not identical; while the Zn^{2+} binding protein may be thionein (*16*), the Cu^{2+} binding protein differs in its amino acid composition from both thionein and chelatin (*17*). Furthermore, there seems to be an inverse relationship between the synthesis of these binding proteins and cation transfer through the intestine (*16, 17*). That interaction between metals at the level of intestinal absorption is more complex than competition for a simple carrier is shown by the diversity of conditions which influence the absorption of lead (*18, 19*).

Metabolic Interference

Cadmium and Hg^{2+} are able to decrease the formation of dimethyl selenide from selenite (*20, 21*) because dimethyl selenide formation has an absolute requirement for GSH (*22*). The reaction of selenite with GSH leads to the formation of selenotrisulfide (*23*). Either this compound, or another metabolite of selenite, becomes bound to plasma proteins, mainly β-lipoprotein and globulins (*24*) and, by an unknown mechanism, promotes the binding of Hg^{2+} and Cd^{2+} to plasma proteins (*14, 15*). It is not known how the metabolism of selenite,

apart from dimethyl selenide formation, is influenced by Hg^{2+} or Cd^{2+} and what is the essential step in the protective effects between selenium and the two heavy metals, but selenium increases the cleavage of C-Hg bond of phenylmercury (*25*). Observations that (a) the toxicity of dimethylselenide is increased by Hg^{2+} (*20*), (b) selenium affects the blood concentration and distribution of methylmercury differently from inorganic mercury (*3, 12*), (c) in tissue cultures $MeHg^{+}$, on a molar basis is fifty times more efficient against the toxicity of selenite than Hg^{2+} (*26*); and (d) lead and selenium have a mutual detoxifying effect (*27*), underline the difficulty in the interpretation of the available biochemical data in relation to the pathological process.

Induction of Protein Binding Sites

Thionein is a low molecular weight protein (MW < 10,000) which is able to incorporate or bind a wide variety of metals: Cd^{2+}, Cu^{2+}, Zn^{2+}, Hg^{2+}, Ag^{2+}, Sn^{2+} (*28*), Co^{2+}, and Bi^{3+} (*29*). The most potent inducers of thionein synthesis are Zn^{2+}, Cd^{2+}, and Hg^{2+} (*30–32*). Cadmium will replace Zn^{2+}, and Hg^{2+} will replace Cd^{2+} in the corresponding metallothionein of the liver (*30*) and kidneys *in vivo* (*32, 33*). Hence interactions between metals that involve thionein can operate through the induction of the protein and through competition for binding on an induced metallothionein. Continuous Cd^{2+} ingestion for example, leads to a considerable increase in the hepatic content of Zn^{2+} and in the renal content of copper bound to thionein (*34*), while copper and zinc thionein can be isolated from the livers of Cu^{2+} injected rats (*35*). If uptake by an organ is increased less than the increase in the thionein bound fraction of the metal, toxicity could be decreased. Pretreatment of female rats with low doses of Cd^{2+}, however gives a maximum protection against lethal doses of Cd^{2+} 1 and 3 days after pretreatment, though increased thionein content and the capacity to synthesize thionein are maintained for a much longer time (*36*). Protection given by Cd^{2+} against a renotoxic dose of Hg^{2+} increases the thionein bound Hg^{2+} in the kidneys, but the increase in the total uptake is higher, partly because large molecular proteins bind more Hg^{2+} (*33*). Thus induction of thionein and the role of thionein in metal induced protection must be carefully analyzed in every instance.

Interaction can produce protection even though the thionein bound fraction of heavy metals is decreased. In the liver, kidneys, and testis, selenium diverts nearly all Hg^{2+} or Cd^{2+} in the soluble fractions from small molecular weight proteins, probably thionein, to larger ones (*37, 38*).

Morphological Factors

Pretreatment with a small but tubulotoxic dose of UO_2^{2+} is able to protect against a subsequent toxic dose. One of the factors in this protection is that the regenerated brush border is more even compared with the normal brush border (*39*). The brush border is replaced by a smooth membrane after the administration of tubulotoxic doses of $HgCl_2$ (*40*), and it is known that in this condition animals can tolerate higher doses of $HgCl_2$ than otherwise (*41*). As those metals which are able to initiate a tolerance are also able to develop cross tolerance (*41*), morphological factors, for example decreased surface area at the part of the tubular cells, where metals are usually taken up, might influence the tubular reabsorption and contribute to their interaction.

Interaction and Synergistic or Antagonistic Effects

Interaction between two metals usually results in a decrease in toxicity. If this effect is associated with a shorter half time or lower concentration in the target organ, at least the last link between protection and interaction is established, even though the mechanism of decrease in half time or organ uptake may be unknown. However, the situation usually is more complex; there is a mutual interaction between metals which depend on a chain of reactions; half time and uptake in the target organ are increased, etc.

The purpose of research in this labyrinth is to establish whether the connection between two effects like chemical interaction and protection is coincidental or casual, and to establish the correct sequence of events leading to antagonistic or synergistic effects.

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